

Effects of Nalbuphine and Nefopam in the Management of Postoperative Shivering after Laparoscopic Cholecystectomy under General Anaesthesia: A Randomised Double-blind Study

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ABSTRACT

Introduction: Postoperative shivering is a very common and unpleasant complication of laparoscopic surgery under General Anaesthesia (GA). Postoperative shivering is uncomfortable for the patient, and it might increase the postoperative complications especially in high-risk patients.

Aim: To compare the therapeutic effects of nalbuphine and nefopam in treating postoperative shivering in patients undergoing Laparoscopic Cholecystectomy (LC) under GA.

Materials and Methods: The present study was a randomised, double-blinded, study conducted in the Department of Anaesthesiology and Surgery on 60 ASA Grade-I and II physical status scheduled for elective LC under GA, who developed postoperative shivering during recovery from GA, at Government Medical College and Hospital, Kathua, Jammu and Kashmir, India. A total of 60 patients aged between 25 to 60 years, American Society of Anaesthesiologists (ASA) I and II scheduled for elective LC under GA, who had postoperative shivering during recovery period. Study duration was of one year (October 2021 to October 2022). Patients were randomly allocated into group A (n=30,

received nalbuphine) and group B (n=30, received nefopam). Data was collected and compiled using Statistical Package for the Social Sciences (SPSS) version 23.0. Student's t-test and Chi-square test was used to analyse the data. The p-value <0.05 was considered as statistically significant.

Results: Time for cessation of shivering was 4.11±1.12 minutes in nalbuphine group as compared to 3.03±0.68 minutes in nefopam group which was statistically significant (p=0.001). Response rate was 73.33% in nalbuphine group as compared to 90% in nefopam group, and the difference was statistically significant (p=0.043). Similar incidence of bradycardia and vomiting was noted in both the groups. Nausea (6.67% vs 3.33%), pain on injection (3.33% vs nil) and pruritis (6.67% vs nil) were more in nalbuphine group as compared to nefopam group which was statistically significant. Sedation was more in nalbuphine group as compared to nefopam group (10% vs 6.67%) which was not significant statistically.

Conclusion: Nefopam as compared to nalbuphine had earlier cessation of shivering, better response rate and had less side-effects.

Keywords: Grades of shivering, Hypothermia, Thermoregulation

INTRODUCTION

Postanaesthetic shivering is defined as an involuntary movement of one or more muscle groups in the early recovery phase following general or regional anaesthesia which is the leading cause of discomfort for postsurgical patients [1]. Postanaesthetic shivering is a common experience among patients recovering from the comforts of modern regional or GA and is even worse than postoperative surgical pain [2]. Postanaesthesia shivering occurs in 20-70% after GA [3]. Most of the times, it is preceded by central hypothermia and peripheral vasoconstriction, indicating that it is almost a thermoregulatory mechanism, which even today is less understood [4]. Shivering is uncomfortable for the patient and also interferes with monitoring in the recovery. Shivering can increase metabolic requirement, which might be deleterious for patients with fixed cardiac output and limited respiratory reserves [5]. Moreover the incidence of shivering is more in laparoscopic surgeries because of the convection effects produced by cool CO₂ (20.1°C) flow inside the peritoneal cavity [6]. There are various methods available to control shivering during anaesthesia, which include non pharmacological methods and pharmacological methods using drugs which have antishivering properties. Non pharmacological methods using equipment such as covering with drapes (by blanket), using radiant heat and warming up operating rooms to

maintain the normal temperature of the body are effective [7]. Other non pharmacological methods which use specialised equipments to prevent or to control shivering are expensive and are not practical in all clinical settings. The pharmacological methods using drugs like pethedine, nalbuphine, tramadol, clonidine, doxapram, katanserin, nefopam, etc., are simple, cost-effective and easy to implement [8,9]. Despite the availability of many drugs, it still continues to be an ongoing problem in Post Anaesthesia Care Unit (PACU).

Nalbuphine is a mixed agonist-antagonist opioid with κ -agonist activity and it antagonises side-effects of μ -agonists [10]. Nalbuphine results in an uncharacteristically large reduction in the shivering threshold than the exaggerated generalised thermoregulatory inhibition [11]. Studies have shown nalbuphine to be better than tramadol in controlling shivering with faster onset and better sedation with less side-effects [12,13]. Nefopam is a non opiate, benzoxazocine substance [14]. Nefopam is a synaptic reuptake inhibitor of dopamine, norepinephrine and serotonin and effects thermoregulatory response via α_2 adrenoceptors [15]. Commonly used drugs for postoperative shivering like tramadol, meperidine have high incidence of side-effects. So, there is a need to find drugs as effective but with less side-effects. Both the study drugs are in use since long as analgesics and both the drugs had been studied differently by many researchers as having antishivering effects after

anaesthesia [16-18]. To the best of the author's knowledge there is hardly any study comparing nalbuphine with nefopam for the control of postoperative shivering. Present study was aimed to compare the therapeutic effects of nalbuphine and nefopam in preventing postoperative shivering in LC under GA.

MATERIALS AND METHODS

Present study was a randomised, double-blinded study, conducted in the Department of Anaesthesiology and Surgery on 60 ASA Grade-I and II physical status scheduled for elective LC under GA, who developed postoperative shivering during recovery from GA, at Government Medical College and Hospital, Kathua, Jammu and Kashmir, India. Study duration was of one year from October 2021 to October 2022. The study was commenced after approval from Institutional Ethical Committee (IEC) (IEC/GMCK/87/Pharma dated 25/8/2021). After explaining the patients in their local language, written consent was taken for participation in the study, during preanaesthetic evaluation.

Inclusion criteria: A total of 60 patients belonging to ASA Grade-I and II of either gender aged 25 to 60 years, who were scheduled for elective LC under GA and developed postoperative shivering during recovery period from GA were enrolled in the study after taking informed consent.

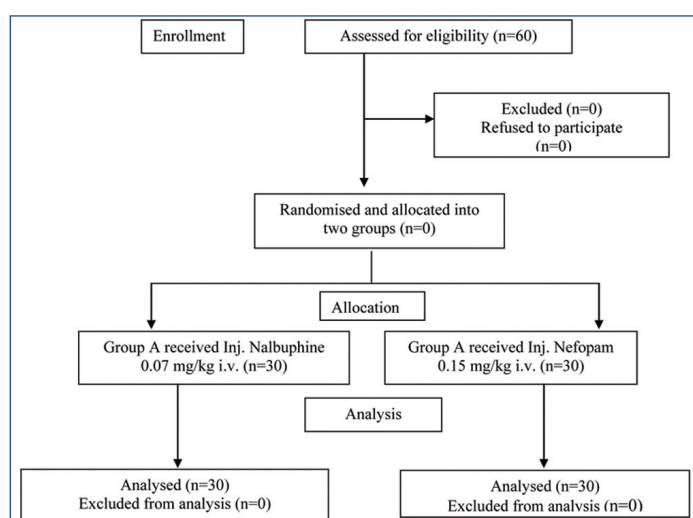
Exclusion criteria: Patients with body temperature more than 37.5°C, allergy to any of the study drug, history of muscular disorders, convulsions and those with body temperature less than 36.5°C at extubation were excluded from the study.

Sample size calculation: Sample size was calculated on the basis of previous studies. Incidence of postoperative shivering was 20-70% [3,19]. A sample size of approximately, 30 in each group was needed to demonstrate the effectiveness of nalbuphine and nefopam in reducing shivering by 50% with 95% confidence (α -0.05) and the power of the study being 80%.

All patients who fulfilled the inclusion criteria were enrolled and randomised using computer generated chart with allocation ratio of 1:1 into either of the two groups.

- Group A (n=30) received intravenous (i.v.) nalbuphine (0.07 mg/kg)
- Group B (n=30) received i.v. nefopam (0.15 mg/kg).

The Consolidated Standards of Reporting Trials (CONSORT) diagram is shown in [Table/Fig-1].



[Table/Fig-1]: CONSORT diagram.

Patient's age (years), weight (Kg), Body Mass Index (BMI) (Kg/m²), gender (male/female), ASA grade were recorded. Induction of anaesthesia was done using propofol 2 mg/kg, vecuronium 0.08 mg/kg and fentanyl (1-2 µg/kg). The trachea of all the patients was intubated with an appropriate sized endotracheal tube, and maintenance of anaesthesia was done with isoflurane

and vecuronium. Neuromuscular blockade was reversed with glycopyrrolate and neostigmine. Warm fluids were used intraoperatively and operating room temperature was maintained at approx 22°C. Basic monitoring was done intraoperatively. In the recovery room, patients were observed for occurrence of shivering and grades of shivering were assessed. Grading of the shivering was carried out by a scale similar to that validated by Crossley AWA and Mahajan RP [20] [Table/Fig-2].

Grades	Clinical signs
0	No shivering
1	Piloerection or peripheral vasoconstriction, but no visible shivering
2	Muscular activity (fasciculation) in only one muscle group
3	Muscular activity in more than one muscle group, but no generalised shivering
4	Shivering involving the whole body, with generalised shaking

[Table/Fig-2]: Grades of shivering [20].

Both the patients and the anaesthesiologist assessing the shivering grades were blinded to the study drug used. Both the study drugs were prepared by another anaesthesiologist who was not involved in the study. Single bolus dose of either i.v. nefopam (0.07 mg/kg) or i.v. nalbuphine (0.15 mg/kg) was given to treat shivering Grade 2, 3, 4. Shivering grade was further evaluated at 10, 20 and 30 minutes after the study drug administration.

All patients in the recovery room were attached to basic monitors and baseline Oxygen Saturation (SpO₂), Heart Rate (HR), Mean Arterial blood Pressure (MAP), and axillary temperature were measured and measurements repeated every 10 minutes. Time to disappearance of shivering noted after administration of either of the study drugs. Response to treatment was considered if shivering ceased within 20 minutes of drug administration, if not it was considered as incomplete response. In the patients with incomplete response, rescue dose of i.v. Tramadol (1 mg/kg) was given. Any adverse side-effects like nausea, vomiting, pruritis, sedation were recorded.

STATISTICAL ANALYSIS

Data was collected and compiled using Microsoft Excel, analysed using SPSS version 23.0. Frequency, percentage, means and Standard Deviations (SD) was calculated for the continuous variables, while ratios and proportions were calculated for the categorical variables. Difference of proportions between qualitative variables was tested using Student's t-test and Chi-square test or Fisher-exact test as applicable. The p-value <0.05 were considered as statistically significant.

RESULTS

In the present study, 60 patients were randomly allocated into group A (n=30, received nalbuphine) and group B (n=30, received nefopam). There was no statistically significant difference (p>0.05) noted in both groups with respect to age (years), weight (Kg), BMI (Kg/m²), gender (male/female), ASA grade and duration of surgery [Table/Fig-3].

General characteristics	Group A (n=30)	Group B (n=30)	p-value (Students' t-test)
Age (years)	43.3±11.3	42.9±12.4	0.65
Weight (kg)	69.1±10.5	67.9±8.7	0.72
BMI (kg/m ²)	23.4±3.1	24.1±2.9	0.75
Gender (M/F)	13/17	14/16	0.69
ASA I/II	20/10	21/9	0.59
Duration of surgery (minutes)	88.1±32.2	92.5±34.2	0.66

[Table/Fig-3]: Demographic data of patients in both group. ASA: American society of anaesthesiologists

Regarding axillary temperature (°C) at baseline, 10, 20 and 30 minutes after the study drug administration were comparable among both

groups and the difference was not statistically significant ($p>0.05$) [Table/Fig-4].

Timeline	Axillary temperature (°C)		p-value (Students' t-test)
	Group A	Group B	
Baseline	35.33±0.53	35.26±0.46	0.332
After shivering (in minutes)			
10	35.27±0.50	35.10±0.56	0.143
20	35.18±0.58	35.09±0.36	0.571
30	34.99±0.37	34.90±0.39	0.160

[Table/Fig-4]: Axillary temperature (°C) of patients in both the groups.

As far as HR (beats per minute) at baseline, 10, 20 and 30 minutes after the study drug administration was concerned, were comparable among both groups and no statistically significant difference was noted ($p>0.05$) [Table/Fig-5].

Timeline	Heart Rate (HR)		p-value (Students' t-test)
	Group A	Group B	
Baseline	76.46±6.17	77.83±6.59	0.106
After shivering (in minutes)			
10	74.96±4.70	74.66±5.61	0.295
20	72.5±5.13	71.8±6.52	0.129
30	72.83±3.92	73±4.07	0.752

[Table/Fig-5]: Heart Rate (HR) of patients in both the groups.

In present study, MAP (mmHg) at baseline, 10, 20 and 30 minutes after the study drug administration were comparable in both groups with no statistically significant difference ($p>0.05$) [Table/Fig-6].

Timeline	Mean Arterial blood Pressure (MAP) (mmHg)		p-value (Students' t-test)
	Group A	Group B	
Baseline	80.5±7.83	79.7±11.32	0.332
After shivering (in minutes)			
10	78.96±7.48	78.46±6.03	0.571
20	79.06±6.35	78.83±10.67	0.160
30	82.2±5.21	81.9±12.35	0.288

[Table/Fig-6]: Mean Arterial blood Pressure (MAP) of patients in both the groups.

In present study, partial pressure of SpO₂ at baseline, 10, 20 and 30 minutes after the study drug administration were comparable in both groups with no statistically significant difference ($p>0.05$) [Table/Fig-7].

Timeline	Partial pressure of Oxygen Saturation (SpO ₂)		p-value (Students' t-test)
	Group A (%)	Group B (%)	
Baseline	98.81±0.74	98.54±0.65	0.77
After shivering (in minutes)			
10	95.97±2.64	96.27±2.98	0.919
20	96.3±1.74	97.0±3.14	0.682
30	98.98±0.92	99.05±0.6	0.60

[Table/Fig-7]: Partial pressure of Oxygen Saturation (SpO₂) of patients in both the groups.

Time for cessation of shivering was 4.11±1.12 minutes in nalbuphine group as compared to 3.03±0.68 minutes in nefopam and difference was statistically significant ($p=0.001$) [Table/Fig-8]. Response rate to shivering was statistically significant ($p=0.043$) [Table/Fig-8]. Incomplete response was statistically significant [Table/Fig-8]. Similar incidence of bradycardia and vomiting was noted in both groups. Nausea (6.67% vs 3.33%), pain on injection (3.33% vs nil) and pruritis (6.67% vs nil) were more in nalbuphine group as compared to nefopam group and difference was statistically insignificant

[Table/Fig-9]. Sedation was more in nalbuphine group as compared to nefopam group (10% vs 6.67%) but difference was not significant statistically [Table/Fig-9].

Parameters	Group A	Group B	p-value (Students' t-test)
Time for cessation of shivering (min)	4.11±1.12	3.03±0.68	0.001
Response rate [^] n (%)	22 (73.33)	27 (90)	0.043
Incomplete response [^] n (%)	8 (26.67)	3 (10)	0.023

[Table/Fig-8]: Final results of shivering in both the groups.
[^](Chi-square test)

Parameters	Group A n (%)	Group B n (%)	p-value (Fisher's test)
Bradycardia	1 (3.33)	1 (3.33)	0.95
Nausea	2 (6.67)	1 (3.33)	
Vomiting	1 (3.33)	1 (3.33)	
Pain on injection	1 (3.33)	0	
Sedation	3 (10)	2 (6.67)	
Pruritus	2 (6.67)	0	

[Table/Fig-9]: Comparison of side-effects and complications in both the groups.

DISCUSSION

The main causes of shivering intra or postoperative are temperature loss, decreased sympathetic tone and systemic release of pyrogens [21]. Intraoperative hypothermia can be minimised by any technique that limits cutaneous heat loss to the environment such as those due to cold operating room, evaporation from surgical incisions and conductive cooling produced by administration of cold iv fluids [22]. Following risk factors predispose the patient to hypothermia and shivering: young age, male gender, low body weight, or poor nutritional status, prolonged preoperative fasting, an ASA grade greater than 1, combined general-regional anaesthesia and the extent of induced sympathetic blockade, administration of premedication, volatile anaesthetics, and muscle relaxants, temperature of operating room and i.v. fluids [23].

The results of present study showed the superiority of nefopam over nalbuphine in the treatment of postoperative shivering as shown by earlier cessation of shivering and higher response rate. Present study findings were in contrast to the study conducted by Megalla SA and Mansour HS who observed that the mean response time for control of shivering in nalbuphine group was 3.56±0.82 minutes with success rate of 92% and relapse rate was 8.7% in patients after spinal anaesthesia [24]. However, in present study response time was 4.11±1.12 minutes with success rate of 73.33% and relapse rate of 26.67%. This could be because of more incidence of shivering after laparoscopic surgery.

Taneja P et al., used nalbuphine in a dose of 0.3 mg/kg for the control of shivering after spinal anaesthesia in caesarean section and observed the response rate to shivering of 90% and recurrence of shivering in 20% of patients [16]. This result was in contrast to present study findings, which could be because present study have used lesser dose of nalbuphine (0.07 mg/kg). Lv M et al., in their meta-analysis observed that prophylactic administration of nefopam significantly reduced the risk of perioperative shivering not only in the patients under GA but also neuraxial anaesthesia (95%), which was slightly more than present study, since present study used nefopam for treatment of postoperative shivering and also noted that nefopam has no influence on the extubation time [25]. In a study by Abdulameer AN et al., they observed that a single bolus dose of nefopam allows the cessation of shivering after surgery in 95% of patients with no recurrent episodes of muscle twitching, nausea, vomiting, sweating, or tachycardia [17]. These findings were quite similar to present study results, where 90% of patients had cessation of shivering after nefopam bolus dose.

Mohamed SH found nefopam better than dexmedetomidine for control of intraoperative shivering with its rapid onset, higher response rate and less side-effect [26]. Alfonsi P et al., showed that nefopam caused a minor increase in the core temperature by decreasing the shivering threshold and without affecting sweating and vasoconstriction threshold, thereby minimising the loss of heat [27]. However, other drugs such as clonidine, meperidine, tramadol reduce both shivering and vascular threshold which leads to greater heat loss. Kranke P et al., on his meta-analysis on medication and dosing practices observed that prophylaxis against perioperative shivering should start with external warming and if not relieved then progress to pharmacological interventions, as pharmacological prophylaxis is not cost-effective [28]. Very few studies were done earlier comparing nalbuphine and nefopam for postoperative shivering after LC under GA, so the present study could be an important source of information for clinical researchers.

Limitation(s)

In present study, sample size was small, and the temperature of intravenous fluids was not monitored.

CONCLUSION(S)

Nefopam as compared to nalbuphine had earlier cessation of shivering, better response rate and less side-effects, thus nefopam should be preferred for management of postoperative shivering after LC under GA. Large sample studies are recommended to confirm present study findings.

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